Monitoring of diabetic dogs

Het monitoren van honden met diabetes mellitus

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ABSTRACT

Diabetes mellitus is one of the most common endocrine disorders in the dog. Although diagnostics are relatively straightforward, treatment and especially adequate long-term monitoring are challenging. To avoid complications, such as hypoglycemia, weight loss, diabetes ketoacidosis and urinary tract infections, adequate monitoring is indispensable. In this review different monitoring tools, such as history and clinical signs, single and serial blood glucose measurements, glycated blood products, continuous glucose measurements and urine glucose will be evaluated. Because each monitoring technique has its limitations, the challenge for the veterinarian is to use an adequate combination of these tools to obtain a good image of the patient's glycemic status.

SAMENVATTING

Diabetes mellitus is één van de meest voorkomende endocriene aandoeningen bij de hond. De diagnose kan vrij eenvoudig gesteld worden, maar de behandeling en voornamelijk het toepassen van een gepaste opvolging vormen een uitdaging. Het goed monitoren is belangrijk om complicaties, zoals hypoglycemie, gewichtsverlies, diabetes ketoacidose en urineweginfecties, te vermijden. Er bestaan verschillende methoden om een diabetespatiënt op te volgen: anamnese en lichamelijk onderzoek, éénmalige glucosebepaling, glucosedagcurves, fructosaminebepaling, geglyceerd hemoglobine, continuë glucosemetingen en glucosurie. De kunst is om aan de hand van een combinatie van deze technieken een goed beeld te krijgen van de glycemische status van de patiënt.

INTRODUCTION

With a prevalence of 0.32% to 0.64%, diabetes mellitus is one of the most common endocrine disorders in middle aged dogs, with a predisposition for female dogs (Guptill et al., 2003; Rand et al., 2004; Davison et al., 2005; Fall et al., 2007).

The diagnosis of diabetes mellitus in the dog is relatively easy and based on three findings: typical clinical signs (polyuria, polydipsia, weight loss, polyphagia), and persistent fasting hyperglycemia and glycosuria (Plotnick and Greco, 1995a; Fleeman and Rand, 2001). The combination of persisting fasting hyperglycemia and glycosuria is essential for the diagnosis of diabetes mellitus. A thorough diagnostic work-up is mandatory to exclude or identify concurrent diseases. This work-up should minimally include a thorough physical examination, including oral inspection and ophthalmic examination, complete blood count, serum biochemistry profile, including thyroxine and canine pancreatic lipase immunoreactivity (cPLI) and urinalysis with culture. If available, an abdominal ultrasound is indicated (Bennet, 2002; Feldman and Nelson, 2004; Monroe, 2009).

Treatment consists of adequate insulin therapy, diet, regular exercise, ovariohysterectomy in intact bitches, discontinuation of medication that causes carbohydrate-intolerance, and treatment of concurrent inflammatory, infectious, hormonal or neoplastic disorders. An essential part of the therapy is maintaining or achieving an ideal body weight. The goal is to eliminate the owner-observed clinical signs, provide a good quality of life and prevent complications such as hypoglycemia (Miller, 1995; Fleeman and Rand, 2001; Feldman and Nelson, 2004). The severity and duration of hyperglycemia are directly correlated with the clinical signs and the development of complications. Therefore, it is important to have an adequate insulin dosage and an appropriate monitoring to fine-tune the therapy (Feldman and Nelson, 2004; Reusch, 2009).

Clinical signs are often suggestive and the diagnosis in dogs is readily confirmed by simple diagnostic tests. The true challenge lies in the adequate treatment and monitoring of the diabetic dog (Bennet, 2002; Van de Maele, 2005). This review only describes the monitoring of patients with non-ketoacidotic diabetes mellitus.

INITIATION OF INSULIN THERAPY

For the treatment of non-ketoacidotic animals, intermediate- or long-acting insulin should be used. The only drug registered for use in dogs is intermediate-acting insulin (lente: Caninsulin®, MSD, Animal Health). This type of insulin must be administered with a 40 international units (I.U.) syringe. The recommended starting dosage is 0.25-0.5 I.U./kg of the optimal body weight twice daily, although most dogs are safely started on 0.5 I.U./kg twice daily (Fleeman and Rand, 2001; Behrend, 2006). The risk of hypoglycemic episodes is higher when insulin is administered once daily, and most dogs need a twice-daily administration for an adequate glycemic control (Hess and Ward, 2000; Fleeman and Rand, 2001; Davison et al., 2005; Monroe et al., 2005; Behrend, 2006).

Newly diagnosed dogs can be closely observed by the owner at home or can be hospitalized for 24 to 48 hours to evaluate the insulin response. During hospitalization, blood glucose concentrations can be measured at the time of administration and three, six and nine hours later, while further diagnostic tests are performed. The goal is to identify dogs that might be at risk for hypoglycemia (Miller, 1995; Fleeman and Rand, 2001; Behrend, 2006). Patients in which the glucose concentration drops below 5.6 mmol/l (100 mg/dl) during the first 24 to 48 hours of monitoring, should be discharged on a dose that is reduced by 25%. Since it takes several days for the diabetic dog to adjust to the insulin dose or type, the dosage in persistently hyperglycemic dogs is not raised until the first recheck five to seven days later (Miller, 1995; Fleeman and Rand, 2001; Monroe et al., 2005; Behrend, 2006).

A crucial part in the initiation of therapy is a good owner communication and education. Dog owners should be aware of the lifelong commitment, feel comfortable administering the insulin, and they should be taught to recognize possible life-threatening complications of the disease. It is important to explain to the owner that it might take at least one to two months to establish an adequate insulin treatment protocol in uncomplicated diabetes mellitus (Fleeman and Rand, 2001; Bennet, 2002; Mathes, 2002).

MONITORING OF DIABETIC CONTROL

Poorly controlled diabetic animals are prone to complications, such as weight loss, diabetes ketoacidosis, urinary tract infections, cataract, etc. The only way to maintain a long-lasting adequate glycemic control is to monitor these animals regularly. The most important criteria are history, clinical signs, serum blood glucose concentration and serial blood glucose curves, serum fructosamine levels, serum glycated hemoglobin concentration, glycosuria and continuous glucose measurement (Miller, 1995; Bennet, 2002; Wiedmeyer and DeClue, 2011). When modifying the insulin dosage, minor adjustments of 10%-25% of the current insulin dosage are advised (Reusch et al., 2010), because hyperglycemia is not immediately dangerous but hypoglycemia may be life-threatening (Miller, 1995). A decrease of 50% is required in case of a Somogyi effect (Reusch et al., 2010). A Somogyi effect is characterized by a rebound hyperglycemia following a hypoglycemic episode or a rapid decrease of blood glucose concentration that evokes the release of diabetogenic hormones, especially epinephrine and glucagon, and a direct hypoglycemia-induced stimulation of hepatic glycogenolysis (Feldman and Nelson, 1982).

In the dose determination period, dogs should be checked every five to seven days. After the appropriate insulin type, dose and dosing interval have been established, the dog should be rechecked one month later. If there is no relapse of clinical signs or signs of hypoglycemia, recheck appointments every three to six months are advised (Bennet, 2002; Monroe et al., 2005).

History and physical examination

Technique

Glycemic control can easily be assessed by evaluating the client's subjective opinion of the severity and evolution of the clinical signs (polyuria, polydipsia, polyphagia, overall health) of his/her dog (Miller, 1995; Wiedmeyer and DeClue, 2011). The veterinarian should instruct the owner to measure the dog's water intake, to document trends in urination frequency, body weight, activity, appetite and vision changes. During the first few months, weekly calls from the owners should be encouraged and ideally they should keep a logbook to help with the long-term monitoring (Bennet, 2002; Van de Maele, 2005). The most reliable clinical parameters are the absence or presence of polyuria, polydipsia, lethargy and weakness. The follow-up of body weight in the medical record is of the utmost importance. Unexpected weight loss and the presence of ketonuria are indicators of poor control. However, their absence does not rule out a poor control. The presence of hepatomegaly or cataract is a poor indicator of the current glycemic control (Briggs et al., 2000).

Pros and cons

The history, combined with the physical examination findings and the evolution of body weight, appears to be a reliable indication for the glycemic control (Briggs et al., 2000). Most of the animals with glucose concentrations between 5.6 and 13.9 mmol/l (100 – 250 mg/dl) are relatively asymptomatic, and the owner is satisfied with the treatment results (Nelson and Couto, 2009). Although the history is an easy and fast way to determine the effectiveness of insulin treatment, it is subjective and its reliability depends largely on the observational skills of the owner (Briggs et al., 2000; Wiedmeyer and DeClue, 2011). The subjectivity of

this evaluation is decreased when combined with other, more objective monitoring tools discussed further (Miller, 1995; Briggs et al., 2000; Feldman and Nelson, 2004). If the history and physical examination are indicative of poor glycemic control, further diagnostics are warranted to define the cause of the poor control (Plotnick and Greco, 1995b; Briggs et al., 2000). Bennet (2002) states that the insulin dosage can be increased in patients with obvious signs of polyuria, polydipsia and polyphagia without further diagnostics. However, this is generally not advised and possibly dangerous, since the clinical signs may also be attributable to the hyperglycemic phase of the Somogyi phenomenon (Feldman and Nelson, 1982). In patients that have no clinical signs, a stable body weight and a normal physical examination, serial blood glucose measurements are probably not necessary. This is especially true if morning pretreatment glucose is between 5.6 and 16.7 mmol/l (100 – 300 mg/dl) (Briggs et al., 2000). In other words, history and physical examination findings that can easily be monitored at home by the client can be used to assist clinical judgments, and are a good indicator of poor glycemic control. Nevertheless, more objective criteria should be evaluated before adjusting the insulin therapy (Briggs et al., 2000; Wiedmeyer and DeClue, 2011).

Single blood glucose measurement

Technique

A single glucose measurement can be performed with a point-of-care analyzer or a portable blood glucose measurement (PBGM) device. Blood can not only be collected through standard venipuncture of the vena jugularis or vena cephalica, but also by puncturing the ear veins (Wess and Reusch, 2000; Bennet, 2002).

Pros and cons

A single blood glucose measurement (BGM) is only useful if hypoglycemia is identified (< 3.3 mmol/l (60 mg/dl)), because in that case the insulin dosage should be decreased. One elevated BGM is not enough to confirm poor glycemic control or to evaluate the effect of a given type and dose of insulin (Nelson and Couto, 2009). An exception can be made for dogs with a history, physical examination and fructosamine concentration indicating good to excellent control. If the pretreatment BGM is between 10 and 15 mmol/l (180 – 270 mg/dl), a serial measurement is probably not necessary and good control can be presumed (Reusch, 2009). Evaluating a BGM alongside a fructosamine or glycated hemoglobin concentration can help with its interpretation. When interpreting a BGM, it is important to know the timing of the dog's last meal and the insulin dose. Bennet (2002) states that a single measurement may be informative when taken at the time of the nadir, determined during a previous blood glucose curve (BGC). However, this is discouraged by Fleeman and Rand (2003), who found a large day-to-day variability in timing of the nadir. Furthermore, a single BGM is highly influenced by stress, excitement, fear or aggressiveness, which may lead to an unreliable measurement (Bennet, 2002; Fleeman and Rand, 2003, Nelson and Couto, 2009).

Fructosamine and glycated hemoglobin

Technique

Fructosamine and glycated hemoglobin are formed by an irreversible, non-enzymatic and non-insulin dependent binding of glucose to serum proteins or hemoglobin, respectively (Armbruster, 1987; Bunn et al., 1976).

Serum fructosamine concentrations reflect the average blood glucose concentration over a period of one to three weeks in dogs (Kawamoto et al, 1992; Reusch et al., 1993; Loste and Marca, 2001). The fructosamine concentration increases parallel with glucose levels, and is far more reliable than a single BGM, since it is not influenced by acute changes due to stress or excitement (Reusch et al., 1993; Marca et al., 2000; Loste and Marca, 2001; Bennet, 2002). Fructosamine is decreased by hypoproteinemia, hypoalbuminemia, hyperlipidemia and azotemia in dogs, and is unreliable in these situations (Kawamoto, 1992; Reusch and Haberer, 2001). Additionally, fructosamine levels should be interpreted with caution in hypothyroid dogs, since they might be elevated due to a reduced protein turnover (Reusch et al., 2002).

Some authors advise to freeze the sample until assayed (Nelson and Couto, 2009). However, this is refuted by Jensen (1992), who proved that 5-day storage at 25°C does not significantly affect the serum fructosamine concentration. The reference interval is laboratory dependent, but is usually around 200-360 µmol/l (Reusch, 2009). An overview of the interpretation is given in Table 1 (for correct interpretation, laboratory specific reference intervals should be used). When interpreting the laboratory result, it should be kept in mind that normoglycemia is not the goal of insulin therapy. Serum fructosamine may therefore be higher in diabetic dogs than in normal, healthy dogs that are used to make up reference intervals (Feldman and Nelson, 2004; Reusch, 2009).

Table 1. Interpretation of the fructosamine concentration in diabetic dogs (adapted from Nelson and Couto, 2009).

Degree of control	Range of fructosamine levels
Excellent control	350-400 µmol/l
Good control	400-450 µmol/l
Fair control	450-500 µmol/l
Poor control	>500 µmol/l
Prolonged hypoglycemia	<300 µmol/l

The glycosylated hemoglobin (GHb) concentration reflects the mean glucose concentration over a period of 10 to 14 weeks in dogs, depending on the life span of red blood cells (Reusch, 2009). As for fructosamine, it is not affected by acute changes and is directly proportional to the glucose level. Anemia will falsely lower the value (Marca et al., 2000; Feldman and Nelson, 2004). GHb is not commonly used in veterinary medicine, due to the large variation in assays and consequently, the wide variation of reference values between laboratories. Moreover, many assays have not been validated for canine patients (Reusch, 2009).

Pros and cons

Serum fructosamine concentration can be used as a screening test for diabetes mellitus, in the routine evaluation of the diabetic dog: 1. when there are discrepancies between history, physical examination and serial blood glucose concentrations, 2. to rule out the effect of stress or excitement on the glucose concentration, 3. to evaluate the response to an insulin dosage change (Jensen, 1994; Jensen, 1995; Loste and Marca, 2001; Feldman and Nelson, 2004). In early diagnosed patients, the fructosamine levels may be normal due to insufficient duration or degree of the hyperglycemia (Reusch and Haberer, 2001). Discrepancies between fructosamine levels on the one hand and clinical signs and blood glucose on the other hand have been observed. In those cases, the veterinarian should rely on the clinical signs to judge the glycemic control (Briggs et al., 2000; Reusch, 2009). Serum fructosamine may be within normal ranges when there are periods of hyper- and hypoglycemia, resulting in a mean glucose concentration within or near the normal range. Elevated fructosamine concentrations indicate insufficient glycemic control, but may be attributable to an inadequate insulin dosage, owner non-compliance or extreme fluctuations in serum glucose levels (e.g. Somogyi phenomenon). Therefore, a fructosamine result does not allow to differentiate between causes of poor glycemic control and does not allow adequate therapy adjustments. Conversely, serum concentrations in the lower half or below the reference interval may indicate significant periods of hypoglycemia (Bennet, 2002; Feldman and Nelson, 2004). Furthermore, serum fructosamine gives no information about the nadir or acute blood glucose changes in response to insulin administration. The soundest approach is to use abnormal serum fructosamine concentrations as an indication of inadequate glycemic control. Subsequently, the BGC can be performed to determine which changes should be made to the insulin protocol (Behrend, 2006; Wiedmeyer and DeClue, 2011).

Since GHb reflects the mean glucose concentration of the previous two to three months, it is not an appropriate parameter in animals that still undergo regular changes the insulin dosage, but it can be used in the follow-up of animals with long-term good control. Elevated concentrations are an indication of poor control, and further diagnostics such as the BGC are needed (Kawamoto et al., 1992; Bennet, 2002). In veterinary medicine, serum fructosamine measurements are commercially more readily available and more practical to use (Feldman and Nelson, 2004; Wiedmeyer and DeClue, 2011). GHb is more sensitive for the detection of hypoglycemia than fructosamine (Loste and Marca, 2001).

Serial blood glucose curve

Technique

When serial glucose measurements are performed while the animal is hospitalized, the normal daily routine of feeding and insulin should be followed. If the dog refuses to eat while hospitalized, the owner can feed the dog at home and bring the animal to the practice right after, since inappetence may seriously influence the results (Fleeman and Rand, 2001; Feldman and Nelson, 2004). To exclude problems with injection proficiency, the owner can administer the insulin while supervised in the practice (Bennet, 2002; Reusch, 2009). The first blood sample should be taken immediately before feeding and injection, or within the hour after doing so (Reusch, 2009). Samples should be taken every one to two hours throughout the day, depending on the type of insulin. In total, monitoring for 12 hours should be sufficient for intermediate acting types of insulin. Twenty-four hours may be required for long-acting insulin types. Longer-acting insulin types tend to have a less predictable peak action (Fleeman and Rand, 2001; Feldman and Nelson, 2004).

Sample collection can be done through standard venipuncture or by an ear prick (Wess and Reusch, 2000; Fleeman and Rand, 2001; Bennet, 2002). Blood glucose concentrations are typically determined by a PBGM device or a point-of-care glucose analyzer (Bennet, 2002; Feldman and Nelson, 2004). Results obtained with the PBGM device generally underestimate the actual glucose level, depending on the device and the degree of glycemia (Wess and Reusch, 2000; Cohn et al., 2000). It is important to consider this error to avoid overdiagnosing hypoglycemia or avoid the misperception that glycemic control is better than it actually is (Wess and Reusch, 2000; Feldman and Nelson, 2004).

In the initial regulation of the diabetic dog, weekly BGC's are mandatory to reach an acceptable glycemic control. In addition, curves are necessary to re-establish glycemic control in dogs with clinical signs of hyperglycemia. History, physical examination, body weight and serum fructosamine determine the necessity of a curve (Bennet, 2002; Behrend, 2006).

The reliability of this technique is patient dependent since anorexia, inactivity, stress, agitation and aggression may influence the glucose level. This should be taken into account when interpreting the BGC. It is important to avoid stress during these check-ups and to prevent aversion towards the veterinarian and his ac-

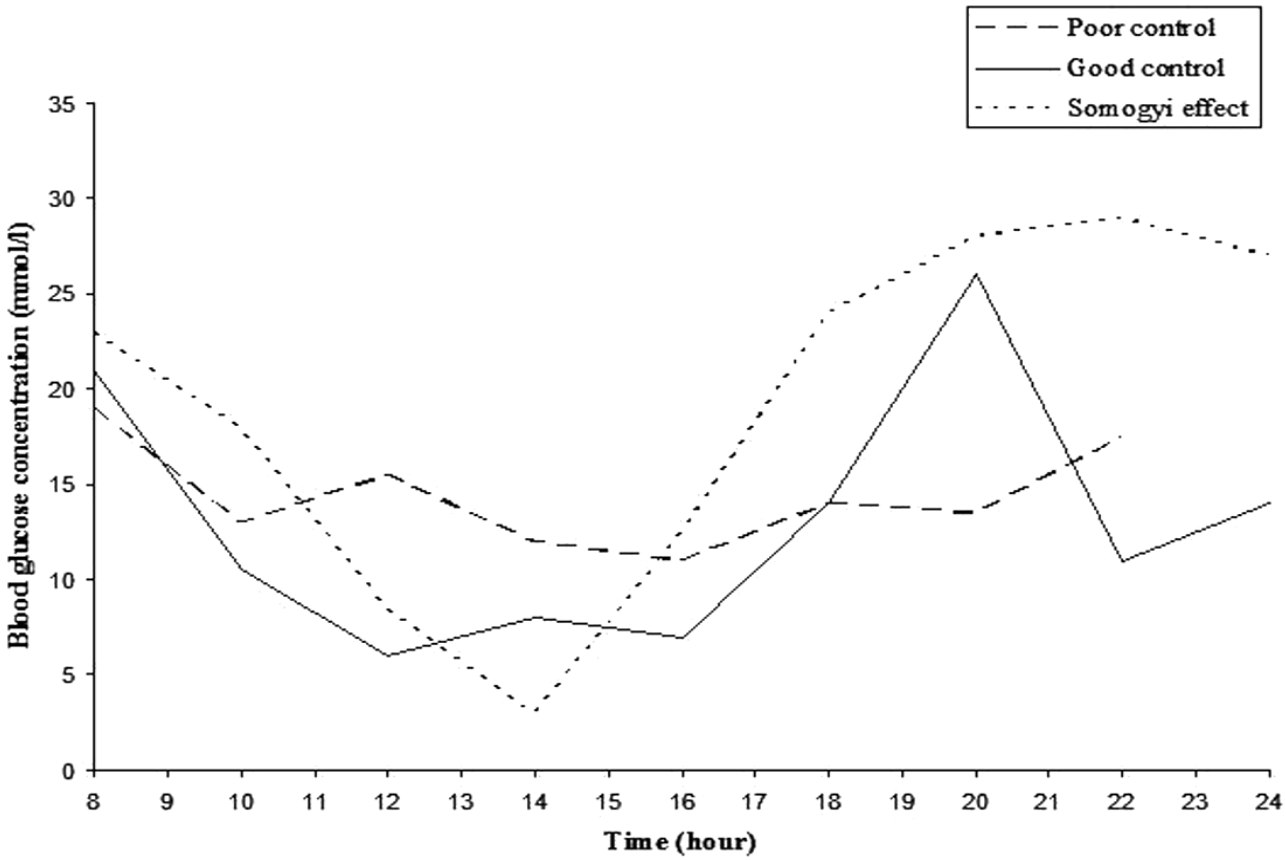

Figure 1. Blood glucose concentration curves obtained from three diabetic dogs treated with a twice-daily insulin protocol, illustrating poor control, good control and the Somogyi phenomenon.
Poor control: the insulin is not effective in lowering the blood glucose concentration; the blood glucose concentration stays above 11 mmol/l.
Good control: the insulin is effective in lowering the blood glucose concentration, the nadir is 6 mmol/l, and the duration of the effect is around 9 to 10 hours.
Somogyi effect: the insulin is effective in lowering the blood glucose concentration, but the nadir is 3 mmol/l; this hypoglycemic episode is rapidly followed by a rebound hyperglycemia

tions, thereby improving the chances of obtaining reliable blood glucose results (Feldman and Nelson, 2004).

Interpretation

Ideally, the blood glucose concentrations should range between 6 and 14 mmol/l (100 – 250 mg/dl) throughout day and night. In most dogs, the highest concentrations occur at the time of each insulin injection. Ideally, the BGC should appear as an inverted bell, with the nadir in the middle (Miller, 1995; Behrend, 2006) (Figure 1).

Three important parameters need to be evaluated consecutively: 1. insulin effectiveness, 2. glucose nadir and 3. duration of effect. The effectiveness is the difference between the maximal and minimal glucose concentration. This difference has to be interpreted in light of the highest glucose concentration and the insulin dosage (e.g. a small difference may be acceptable if the insulin dosage or the highest glucose concentration is low, but not if the dosage or the maximal concentration is high) (Miller, 1995; Nelson and Couto, 2009). The nadir should be between 4.4 and 8.3 mmol/l (80 – 150 mg/dl). If this value is lower or higher, the dosage should be decreased or increased, respectively (Nelson and Couto, 2009). A low nadir may be due to insulin overdosage, excessive overlap of insulin action, insufficient food intake or excessive exercise. Underlying causes of a high nadir may be insulin underdosage, technical problems with insulin administration, the counterregulatory phase of the Somogyi phenomenon, stress, hyperglycemia or insulin resistance (Reusch, 2009). The duration of effect is the time from the injection until the glucose concentration rises above 13.9 – 15 mmol/l (250 – 270 mg/dl). This should be around 10 to 14 hours. If the duration is too short, switching to longer acting insulin every 12 hours or shorter acting insulin three times a day, is recommended. If the effect lasts longer than 14 hours, a shorter acting insulin or a once-daily administration can be considered. The duration may be falsely decreased if the nadir is less than 4.4 mmol/l (80 mg/dl) or if blood glucose declined rapidly, due to the possible Somogyi effect (Miller, 1995; Behrend, 2006; Nelson and Couto, 2009; Reusch, 2009). An overview of the interpretation is given in Figure 2.

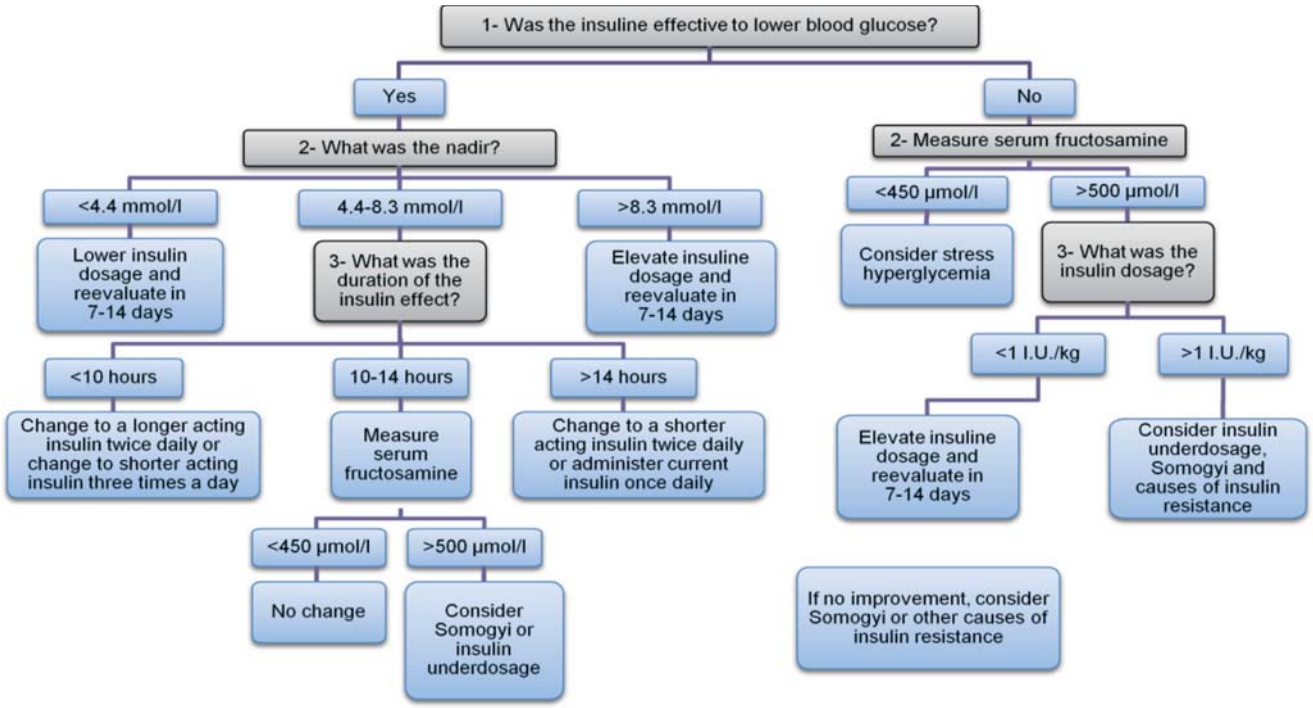

Figure 2. Algorithm for interpreting results of a blood glucose concentration curve (adapted from Nelson and Couto, 2009).

Pros and cons

The evaluation of the BGC demonstrates the pharmacology of the insulin in a particular dog. It provides knowledge of the adequacy of the insulin dosage, the duration of the insulin effect, the nadir, the client compliance, injection timing, insulin resistance and client injection proficiency. Unlike the previously described monitoring techniques, the evaluation of the BGC enables the veterinarian to identify the cause of poor glycemic control. BGC's are a good tool for fine-tuning the insulin therapy in dogs (Bennet, 2002; Van de Maele, 2005; Behrend, 2006; Wiedmeyer and DeClue, 2011).

The blood glucose curve is easy to perform, accurate, and is considered to be the gold standard. Unfortunately, hospitalization, restraint, repeated venipunctures or ear pricks do not only make this a time consuming and expensive technique, they also influence the patient's blood glucose concentration (Miller, 1995; Wess and Reusch, 2000; Wiedmeyer and DeClue, 2011). For these reasons, BGC's are sometimes difficult to perform, hard to interpret and might not always correlate with the real-life glycemic control (Wiedmeyer and DeClue, 2011). Fleeman and Rand (2003) demonstrated a marked day-to-day variability in BGC's of two consecutive days. This is probably attributable to fluctuations in the postprandial glycemic response, the variable absorption rate from the injection site, an inherent error with the dosing syringe, variation in activity or whereabouts and variable sensitivity to insulin. This finding has important clinical implications, especially in well-controlled dogs, leading to the assumption that additional indicators for glycemic control should be evaluated when adjusting the insulin protocol. When interpreting a curve, the history, clinical signs and other parameters such as fructosamine should always be considered in the evaluation of the efficiency of glycemic control over a certain period of time (Miller, 1995; Hess and Ward, 2000; Bennet, 2002; Fleeman and Rand, 2003). Another problem is the reliability of the PBGM device, which depends on the analytical performance of the device, the quality of the test strip and the proficiency of the operator (American Diabetes Association, 1996; Cohn et al., 2000).

In the past, serial blood glucose measurements were always performed in the veterinary practice or the hospital, but for some years now, home monitoring has gained popularity. Home monitoring of blood glucose concentration and continuous glucose monitoring are good alternatives to avoid complications that can occur with BGC's performed at the hospital (Fleeman and Rand, 2001; Davison et al., 2003; Wiedmeyer and DeClue, 2011).

Home monitoring of blood glucose concentration

Technique

Capillary or venous blood can easily be obtained from the ear with a lancet designed for finger-pricks in humans or a small-gauge needle. Subsequently, the glucose measurement is done with a PBGM device (Casella et al., 2003; Van de Maele, 2005). Pre-warming of the ear with a hair dryer improves the blood drop formation (Wess and Reusch, 2000). It is important that the owner feels comfortable with the procedure. Therefore, a gradual introduction to the idea of home monitoring, a good explanation of the technique and the possibility to contact the veterinarian if problems oc-

cur, are key to a successful outcome (Casella et al., 2003; Reusch, 2009).

Pros and cons

In hospitalized dogs, there is an obvious influence of stress, excitement and aggression on the BGC, which can largely be prevented by performing the BGC at home. An important problem within the hospital environment is the lack of appetite, which can effectively be avoided by using home monitoring. A study of Casella et al. (2003) showed that therapy adjustments based on hospital curves differed from those based on home curves in 42% of the cases, but only in 3% they would have been reversed (increase versus decrease of the insulin dosage). Major difficulties which owners may encounter are: resistance of the pet, the need for a second person, the need for multiple punctures (due to technical problems or pet resistance), insufficient blood drop, inadequate absorption of the blood drop, the need for an additional strip, problems with the PBGM device and a visible puncture site afterwards (Casella et al., 2003; Van de Maele, 2005). Studies have shown that the majority of pet owners are willing and able to perform curves and that they are pleased with the result, provided that they are motivated and initially receive an adequate explanation (Casella et al., 2003; Van de Maele, 2005). Long-term owner compliance is good, and although they should be warned not to adjust the insulin therapy without veterinary advice, only a minority of owners change the therapy independently (Reusch, 2009; Wiedmeyer and DeClue, 2011). A disadvantage is the day-to-day variability of BGC's performed at home, which can however be minimized by performing two home BGC's on consecutive days (Fleeman and Rand, 2003; Reusch, 2009).

Continuous glucose monitoring

Technique

Continuous glucose measurement systems measure the glucose concentration in the subcutaneous interstitial fluid using subcutaneous probes or wires. The preferred localization is the lateral thoracic region (Figure 3). An enzymatic reaction generates an electrical signal proportional to the interstitial glucose concentration (Wiedmeyer et al., 2003; Affenzeller et al., 2010). This technique has been used in human medicine for some years, and has now been adjusted for veterinary use (Gross and Mastrototaro, 2000; Wiedmeyer et al., 2003). Measurements take place every three to five minutes, depending on the device, and the system can remain in place for several days. Some devices have real time view of the glucose data, and results can be downloaded from the recording device, providing a detailed glucose profile over a period of time (Wiedmeyer et al., 2003; Wiedmeyer and DeClue, 2008; Affenzeller et al., 2010).

Pros and cons

Continuous glucose monitoring is a good alternative to BGC's. The interstitial fluid glucose concentration correlates well with the blood glucose concentration and the device records even abrupt changes in glucose concentration with a slight delay of five to twelve minutes (Gross and Mastrototaro, 2000; Davison et al., 2003; Wiedmeyer et al., 2003). Digital filters may correct for this delay, but Rebrin et al. (1999) state that this is not necessary for slower glucose dynamic changes. Since the subcutaneous probe remains in place, multiple punctures are avoided, the technique is minimally invasive, and hospitalization and restraint are not necessary. Continuous assessments of the blood glucose concentration are obtained, thus facilitating the detection of brief hypoglycemic periods and overnight monitoring. Consequently, a global image of the dog's glycemic status is generated during its normal day-to-day routine, so sound adjustments in the insulin therapy can be made if necessary (Davison et al., 2003; Wiedmeyer et al., 2003; Wiedmeyer and DeClue, 2008; Fleeman, 2011). As the system may remain in place for up to three days, it can take into account the day-to-day variability noted with BGC's (Fleeman and Rand, 2003; DeClue et al., 2004). Generally, the system is well tolerated, and the removal of the device only causes mild discomfort (Wiedmeyer et al., 2003; Affenzeller et al., 2011).

A mild drawback of this technique is the need for a 1-hour initialization period and calibration requiring blood samples three times a day. Depending on the device, these blood glucose measurements have to be evenly spaced in time or not, but the first sample has to be taken as soon as the initialization period is over. Calibration measurements can be performed with a PBGM device by the owner or by the veterinarian (DeClue et al., 2004). Other disadvantages of this system include high purchase costs, possible detachment from the skin, foreign body reaction, calibration errors and the device's limited range (e.g. Guardian Real-Time; Medtronic: 2.2 - 22 mmol/l). The last makes this technique less reliable in animals with marked hyper- or hypoglycemia, which are unfortunately the patients that would benefit most from continuous monitoring.

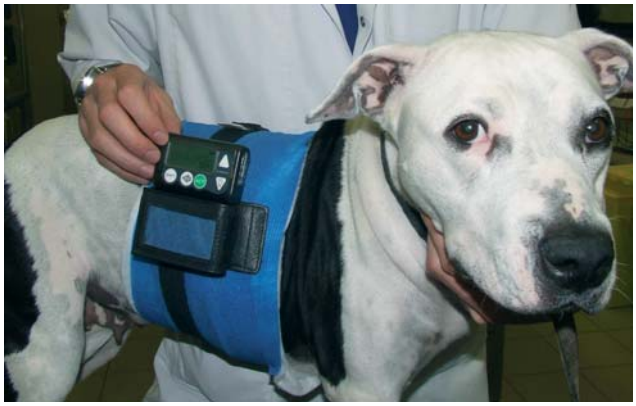

Figure 3. Diabetic dog wearing a continuous glucose monitoring device (Guardian Real-Time; Medtronic).

Furthermore, calibration is impossible when the glucose concentration is beyond this range (Davison et al., 2003; Wiedmeyer et al., 2003; DeClue et al., 2004; Wiedmeyer and DeClue, 2008). These disadvantages may cause difficulties when the animals are not hospitalized. However, the initialization period, the need for calibration and the range are device dependent. A new system based on microdialysis (GlucoDay; Menarini Diagnostics) has been tested. It requires only two calibration sessions (soon after attachment and right before removal), and the glucose concentration range is wider (1.1 – 33.3 mmol/l). Disadvantages are the system's relatively large size, the fact that there is no wireless system available, and that it does not provide real-time display of the glucose concentration (Affenzeller et al., 2010; Fleeman, 2011). Davison et al. (2003) noted that there are discrepancies between blood and interstitial glucose concentrations measured by a classical device (MiniMed; Medtronic) one to three hours after the meal, but overall, the correlation is good, although the interstitial values are generally slightly lower. The devices are designed for human use and the error signal is not particularly audible from a distance. This may result in a loss of data when the error is not noted in time (Davison et al., 2003).

Glycosuria

Technique

Urine can readily be obtained in dogs; if necessary, a long-handled cup or a flat pie pan may facilitate the collection (Miller, 1995). Glycosuria (and ketonuria) can easily be determined semi-quantitatively with a dip stick. In a well-controlled diabetic dog, the absence of glycosuria alternates with periods of glycosuria throughout the day. If used, the interpretation should be based on multiple measurements throughout the day or measurements made over three consecutive days to monitor the trend (Bennet, 2002; Feldman and Nelson, 2004, Reusch, 2009). Bennet (2002) advises daily checks during the initial treatment period, and once the animal is well regulated, this can be reduced to once weekly (Fleeman and Rand, 2001).

Pros and cons

Urine glucose measurement can be used in diabetic bitches after ovariohysterectomy to evaluate whether insulin therapy remains necessary. Moreover, it may be helpful in dogs with recurring hypoglycemia (or ketosis) (Feldman and Nelson, 2004). The urine glucose concentration cannot be used alone to adjust the insulin dosage (Miller, 1995; Bennet, 2002; Monroe, 2009). Consistent severe glycosuria, the presence of ketones or persistent absence of glycosuria demonstrate the need for blood glucose evaluation. It is important to consider that an insulin overdosage may result in the Somogyi phenomenon and in a persistent hyperglycemia and glycosuria for 24 to 72 hours (Miller, 1995; Nelson and Feldman, 2004). Increasing the insulin dosage based on glycosuria in the latter situation will only result in more severe hypoglycemia, more pronounced rebound hyperglycemia and even worse glycemic control. Owners may not adjust the insulin dose based on the result of morning urine glucose, except for a dose decrease for dogs that have recurrent episodes of hypoglycemia and permanent absence of glycosuria (Bennet, 2002; Nelson and Couto, 2009). Urine glucose measurement is an easy and inexpensive alternative to the home BGC, but it does not provide detailed information about the blood glucose concentration, nor does it determine the nature of poor glycemic control (Schaer, 2001, Wiedmeyer and DeClue, 2011). Important shortcomings are that 1. the test is semi-quantitative ; 2. urine collection is not always easy; 3. a negative test does not differentiate between hypo-, normo- or mild hyperglycemia; 4. hydration status and urine concentration affect the result; 5. it does not reflect the blood glucose level at any given time, since the bladder stores urine (Schaer, 2001; Reusch, 2009). Urine glucose measurement serves as an alert system for problems in the glycemic control, but this method should be combined with an evaluation of the clinical signs, the BGC and serum fructosamine concentration before adjusting the therapy (Miller, 1995; Schaer, 2001).

CONCLUSION

Adequate monitoring of the diabetic patient is a challenge. Different monitoring techniques are available, but each of the described techniques has its limitations when used individually. Sound insulin therapy changes should be based on a combination of diagnostic tests and the evaluation of the animal's clinical status.

Owners play a crucial role in the treatment and monitoring of the diabetic dog. They should continuously evaluate their pets for recurrence of clinical signs or complications. After the initiation of the insulin therapy, the animal should be evaluated weekly by a veterinarian for approximately one month. At these controls, body weight evolution and clinical signs are evaluated, and the BGC is performed. The serum fructosamine concentration can be evaluated three weeks to one month after the initiation (or adjustment) of the insulin therapy. When glycemic control is adequate, patients should be evaluated every 3 to 6 months. At these check-ups, history, physical examination, body weight and serum fructosamine are evaluated. When poor control is suspected, the BGC is performed to identify the problem and adjust the therapy accordingly. Since diabetic animals, and especially those with poor control, are at risk for urinary tract infections, a urine culture should be performed once or twice a year.

Single blood glucose measurements are not useful in long-term monitoring and can only be used to modify the insulin therapy if hypoglycemia is detected. Owners can determine the urine glucose concentration

once weekly, which can serve as an alert system for the need for further evaluation of the glycemic control. Serum fructosamine represents a reflection of the average blood glucose concentration of one to three weeks and is an important tool in the monitoring of the diabetic dog. Fructosamine is especially useful as an indicator of inadequate glycemic control, and hence of the need for a BGC or continuous glucose monitoring before adjusting the therapy.

The BGC has been used as the gold standard to determine glycemic control for years, but it also has disadvantages. The most important drawbacks are the fact that it is time consuming, subject to hospitalization related influences and day-to-day variability. A good alternative is teaching the owner to perform the curves at home in order to get a more reliable image of the dog's glycemic status. Continuous glucose monitoring provides an even better global picture, although hospitalization is often required due to the technical difficulties with the device. Detailed knowledge of the blood glucose concentration changes throughout the day, provided by the BGC (performed in the hospital or at home) or continuous glucose monitoring, is necessary to determine the cause of poor glycemic control and to make sound adjustments to the insulin therapy.

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